

(12) UK Patent Application (19) GB (11) 2 361 185 (13) A

(43) Date of A Publication 17.10.2001

(21) Application No 0008791.6

(22) Date of Filing 10.04.2000

(71) Applicant(s)

Nicholas J Wald
22 Staverton Road, OXFORD, OX2 6XJ,
United Kingdom

Malcolm R Law
8 Grosvenor Gardens, LONDON, SW14 8BY,
United Kingdom

(72) Inventor(s)

Nicholas J Wald
Malcolm R Law

(74) Agent and/or Address for Service

Carpmaels & Ransford
43 Bloomsbury Square, LONDON, WC1A 2RA,
United Kingdom

(51) INT CL⁷

A61K 31/60 // A61P 9/10

(52) UK CL (Edition S)

A5B BJA B42Y B421 B43Y B430 B431 B46Y B461 B462
B48Y B481 B482 B49Y B490 B491 B50Y B500 B501
B502 B51X B51Y B510 B52Y B523 B54Y B541 B55Y
B552 B556 B56Y B565 B57Y B576 B58Y B586 B65X
B65Y B650 B66X B66Y
U1S S2415

(56) Documents Cited

WO 98/19690 A1 WO 98/11896 A1 WO 97/38694 A1
Chemical Abstracts No 131:153567 & C.D.Forbes et al,
Semin. Thromb.Haemostasis, (1999), 25(2), 55-9
Chemical Abstract No 129:339684 & C.Spaulding et al,
Circulation, (1998), 98(8), 757-765

(58) Field of Search

UK CL (Edition R) A5B BJA
ONLINE: CAS-ONLINE, EPODOC, JAPIO, WPI

(54) Abstract Title

Pharmaceutical formulation for the prevention of cardiovascular disease

(57) A formulation for the prevention of cardiovascular disease, in particular ischaemic heart disease and stroke, the use of said formulation and a method of preparing said formulation.

The said formulation is a combination of medicines contained in a single formulation for use in the prevention of cardiovascular disease, notably ischaemic heart disease (including heart attacks) and stroke among the general adult population. The said formulation comprises active principals from at least two of the following four categories of drugs or agents:

- i) a blood pressure lowering agent;
- ii) a lipid-regulating agent;
- iii) a platelet function altering agent; and/or
- iv) a plasma/serum homocysteine lowering agent.

GB 2 361 185 A

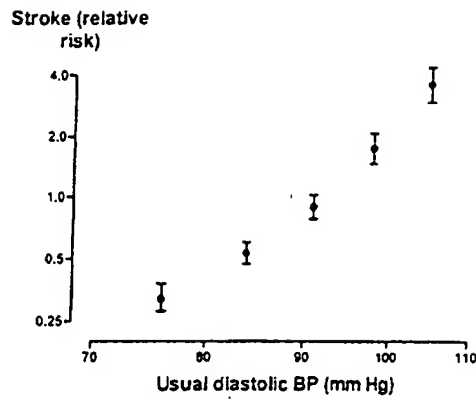


Fig. 1

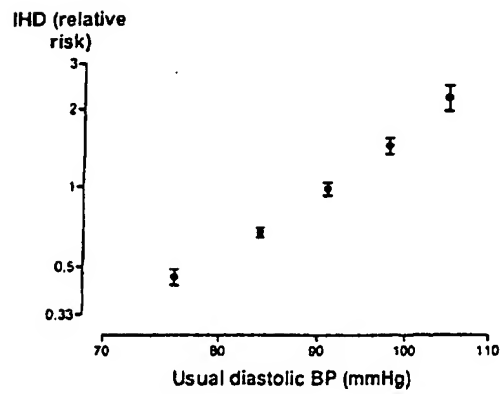


Fig. 2

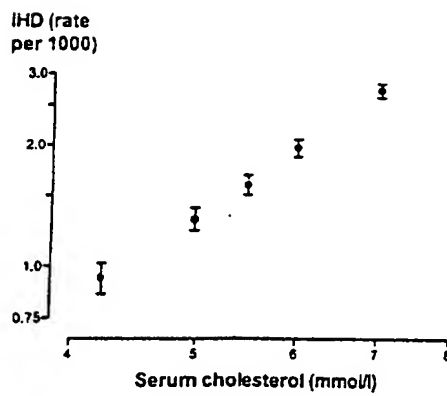


Fig. 3

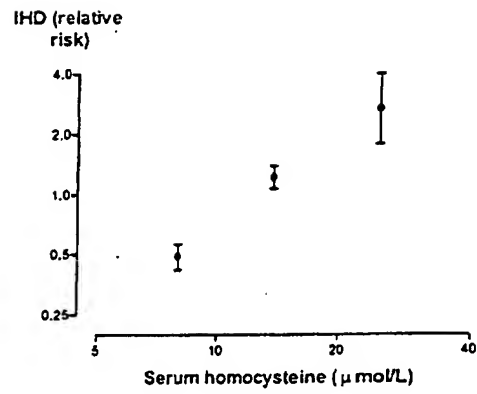


Fig. 4

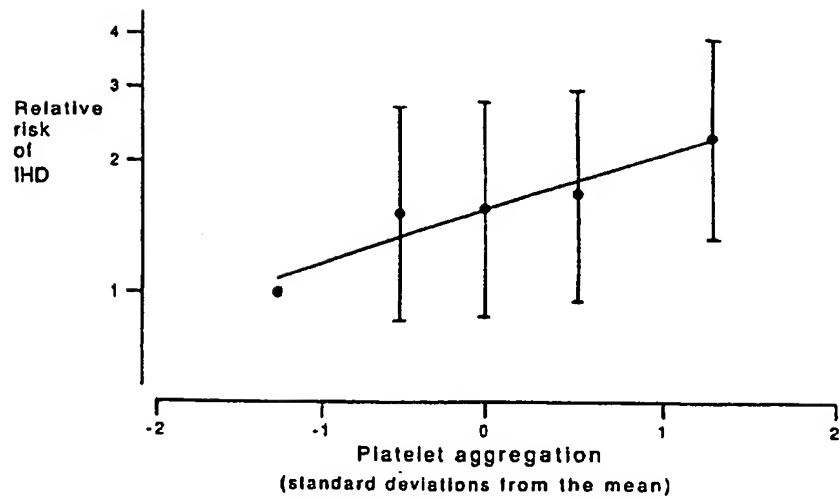


Fig. 5

Formulation for the Prevention of Cardiovascular Disease

This invention relates to a formulation for the prevention of cardiovascular disease, in particular ischaemic heart disease and stroke, the use of said formulation and a method of preparing said formulation.

The formulation of the present invention is a combination of active principals contained in a single formulation for use in the prevention of cardiovascular disease, notably ischaemic heart disease (including heart attacks) and stroke among the general adult population. The formulation of the present invention comprises active principals from at least two of the following four categories of drugs or agents:

- i) a blood pressure lowering agent;
- ii) a lipid-regulating agent;
- 15 iii) a platelet function altering agent; and/or
- iv) a plasma/serum homocysteine lowering agent.

Ischaemic heart disease and stroke constitute the main causes of death in most economic developed countries, accounting for about a third of all adult deaths. Table 1 shows the numbers of deaths from heart disease and stroke in England and Wales in 1998, and also

Cause of death (ICD-9 code)	Men		Women	
	No of deaths	% of all deaths	No of deaths	% of all deaths
Ischaemic heart disease (410-4)	66009	25%	55024	19%
Stroke (430-8)	21432	8%	36046	13%
Heart failure (428), myocardial degeneration (429.1) and hypertensive disease (401-5)	5149	2%	9172	2%
Aortic aneurysm (441)	5829	2%	3668	1%
Total	98419	38%	103914	36%

Table 1 - Numbers of deaths from specified cardiovascular causes in men and women aged 15 and over, and the corresponding proportions of all deaths in men and women aged 15 and over, England and Wales 1998.

the smaller numbers of deaths from other cardiovascular causes that relate to the major cardiovascular risk factors. In total there are 200,000 deaths per year.

The main environmental causes of these diseases, apart from cigarette smoking, are conditions that increase blood pressure, increase serum cholesterol, increase plasma/serum homocysteine, or impair platelet function. The present policy for reducing the incidence of cardiovascular diseases in the general population is based on intervention only when the level of one of these risk factors (especially blood pressure) is found to be particularly high (approximately the top 5% of the distribution in middle aged people and the top 10% in elderly people). Drugs have tended to be used specifically for the control of high values of each risk factor: an individual found to have what is regarded as high blood pressure but an average serum cholesterol concentration will be given treatment to lower the blood pressure but not to lower the serum cholesterol. Drugs to alter platelet function (aspirin) and to lower homocysteine (folic acid) are rarely recommended for healthy persons. In persons who have had a non-fatal heart attack or stroke, treatment aimed at lowering blood pressure is given only if the blood pressure is at a level regarded as high (about top 10%), cholesterol lowering treatment is given if serum cholesterol is in roughly the upper half of the distribution, aspirin is routinely given, folic acid is generally not given.

The proposition underlying this invention is that this policy is inefficient. In seeking to identify persons who will have a heart attack or stroke, identifying only persons with especially high values of risk factors has a limited impact, because most cases of myocardial infarction and stroke occur in persons with risk factors close to the population average. Importantly, the average values of serum cholesterol, blood pressure and homocysteine in Western populations are high compared with the values in populations in which heart disease and stroke are rare. Also, treating persons in the top 5% or so of a distribution cannot make a significant impact on a group of diseases common enough to cause a third of all deaths. In offering treatment to reduce the risk of a heart attack or stroke, reducing each of these risk factors in isolation has a limited impact on the potential for reducing risk. Heart disease and stroke are common in Western countries, because the average values of all the important risk factors are high and their effects, being independent of each other, interact in a multiplicative or synergistic manner. A combined

treatment regimen aimed at changing several risk factors is necessary to achieve a substantial reduction in risk.

The formulation of the present invention comprises active principals from at least two of
5 the following four different categories of drugs or agents:

- i) a blood pressure lowering agent; preferably a diuretic, a beta-adrenoceptor antagonist (abbreviated beta blocker), an angiotensin-converting enzyme inhibitor (abbreviated ACE inhibitor), an angiotension-II receptor antagonist, a vasodilator antihypertensive drug, and/or a calcium-channel blocker; most preferably a
10 diuretic, and/or a beta blocker and/or an ACE inhibitor;
- ii) a lipid-regulating agent such as a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (abbreviated HMG CoA reductase inhibitor), also called a statin;
- iii) a platelet function altering agent; preferably aspirin; and/or
- 15 iv) a plasma/serum homocysteine lowering agent; preferably folic acid.

The proposal to combine these four different categories of drugs into a single formulation is novel. No formulation is currently available that contains more than one category of these drugs in a single formulation. Currently available formulations combine two drugs
20 that both lower blood pressure - thiazide diuretics and beta blockers, and thiazide diuretics and ACE inhibitors. No formulation is currently available that combines drugs that change different cardiovascular risk factors.

The physiological effects of these four different categories of drugs in reducing the risk of
25 cardiovascular disease have been found to be independent of each other. The recognition of the combined effect of using these four different categories of drugs together is novel.

At the preferred dosages of these drugs the prevalence of the ratio of benefit to hazard, i.e. the ratio of the reduction in the incidence of cardiovascular disease to adverse effects of the
30 drugs, is high. The estimation of the preventive effect of the formulation of the present invention and its application in a preventive setting is novel. In fact, a policy of treating a majority of the general population preventively against cardiovascular disease is contrary to the present policy for reducing the incidence of cardiovascular disease, which is based

on intervention only on one of the risk factors when the level of that risk factor is found to be particularly high.

Accordingly, the present invention provides a formulation comprising active principals
5 from at least two of the following four categories:

- i) at least one blood pressure lowering agent,
- ii) at least one lipid-regulating agent,
- iii) at least one platelet function altering agent, and/or
- iv) at least one plasma/serum homocysteine lowering agent.

10

Preferably the formulation comprises active principals from two of the four categories; more preferably the formulation comprises active principals from three of the four categories; most preferably the formulation comprises active principals from all four categories. Optionally the formulation comprises more than one active principal from one
15 or more of the four categories.

20

Preferably the blood pressure lowering agent is a diuretic, a beta blocker, an ACE inhibitor, an angiotension-II receptor antagonist, a vasodilator, and/or a calcium-channel blocker; more preferably the blood pressure lowering agent is a diuretic, and/or a beta
20 blocker, and/or an ACE inhibitor.

25

Preferably the diuretic is a thiazide or thiazide-like diuretic. Preferably the thiazide thiazide-like diuretic is hydrochlorothiazide, chlorthalidone, indapamide, bendroflumethiazide, chlorothiazide, metolazone, cyclopenthiazide, polythiazide, mefruside, or xipamide. Most preferably the thiazide or thiazide-like diuretic is hydrochlorothiazide. Thiazide or thiazide-like diuretics are categorised in the British National Formulary Section 2.2.1 and other equivalent national formularies or pharmacopoeias. Preferably the hydrochlorothiazide is administered in an amount of from about 2.5 mg to about 62.5 mg per day; more preferably the hydrochlorothiazide is
30 administered in an amount of from about 5 mg to about 37.5 mg per day; most preferably the hydrochlorothiazide is administered in an amount of about 12.5 mg per day.

Preferably the beta blocker is a β_1 -selective adrenoceptor antagonist; preferably the β_1 selective adrenoceptor antagonist is atenolol, bisoprolol, betaxolol, metoprolol, celiprolol, or acebutolol. Alternatively the beta blocker is a non-selective beta-adrenoceptor antagonist; preferably the non-selective beta-adrenoceptor antagonist is pindolol, 5 propranolol, oxprenolol, sotalol, timolol, or nadolol. Alternatively the beta blocker is a drug with combined β - and α -adrenoceptor blocking action; preferably this drug is carvedilol, or labetolol. Most preferably the beta blocker is atenolol. Beta blockers are categorised in the British National Formulary Section 2.4 and in other equivalent national formularies or pharmacopoeias. Preferably the atenolol is administered in an amount of 10 from about 5 mg to about 125 mg per day; more preferably the atenolol is administered in an amount of from about 10 mg to about 75 mg per day; most preferably the atenolol is administered in an amount of about 25 mg per day.

Preferably the ACE inhibitor is enalapril, perindopril, captopril, cilazapril, trandolapril, 15 fosinopril, quinapril, lisinopril, ramipril, or moexipril. Most preferably the ACE inhibitor is enalapril. ACE inhibitors are categorised in the British National Formulary Section 2.5.5.1 and in other equivalent national formularies or pharmacopoeias. Preferably the enalapril is administered in an amount of from about 1 mg to about 25 mg per day; more preferably the enalapril is administered in an amount of from about 1.5 mg to about 15 mg 20 per day; most preferably the enalapril is administered in an amount of about 5 mg per day.

Preferably the angiotension-II receptor antagonist is losartan. Angiotension-II receptor antagonists are categorised in the British National Formulary Section 2.5.5.2 and in other equivalent national formularies or pharmacopoeias. Preferably the losartan is administered 25 in an amount of from about 5 mg to about 125mg; more preferably the losartan is administered in an amount of from about 10 mg to about 75 mg per day; most preferably the losartan is administered in an amount of about 25 mg per day.

Preferably the vasodilator antihypertensive drug is hydralazine. Vasodilator 30 antihypertensive drugs are categorised in the British National Formulary Section 2.5.1 and in other equivalent national formularies or pharmacopoeias. Preferably the hydralazine is administered in an amount of from about 2.5 mg to about 62.5 mg per day; more preferably

the hydralazine is administered in an amount of from about 5 mg to about 37.5 mg per day; most preferably the hydralazine is administered in an amount of about 12.5 mg per day.

Preferably the calcium-channel blocker is amlodipine. Calcium-channel blockers are
5 categorised in the British National Formulary Section 2.6.2 and in other equivalent national formularies or pharmacopoeias. Preferably the amlodipine is administered in an amount of from about 0.5 mg to about 12.5 mg per day; more preferably the amlodipine is administered in an amount of from about 0.8 mg to about 7.5 mg per day; most preferably the amlodipine is administered in an amount of about 2.5 mg per day.

10

The most preferred doses named above are half of the doses at the lower end of the therapeutic range recommended in the British National Formulary. This is in order to maximise the therapeutic benefit of the combination of agents, while minimising the risks of adverse effects of the individual agents.

15

Preferably the formulation of the present invention comprises more than one blood pressure lowering agent. Preferably the formulation comprises one or more blood pressure lowering agents selected from a diuretic, a beta blocker, and/or an ACE inhibitor. More preferably the formulation comprises two blood pressure lowering agents selected from a
20 diuretic, a beta blocker, and/or an ACE inhibitor. Most preferably the formulation comprises three blood pressure lowering agents selected from a diuretic, a beta blocker, and an ACE inhibitor.

Preferably the lipid-regulating agent is a serum cholesterol lowering agent. Preferably the
25 serum cholesterol lowering agent is a statin. Preferably the statin is atorvastatin, simvastatin, cerivastatin, fluvastatin, or pravastatin. Most preferably the statin is atorvastatin. Lipid-regulating drugs are categorised in the British National Formulary Section 2.12 and in other equivalent national formularies or pharmacopoeias. Preferably the atorvastatin is administered in an amount of from about 2 mg to about 50 mg per day;
30 more preferably the atorvastatin is administered in an amount of from about 3 mg to about 30 mg per day; most preferably the atorvastatin is administered in an amount of about 10 mg per day.

Preferably the platelet function altering agent is aspirin, ticlopidine, dipyridamole, clopidogrel, or a glycoprotein IIb/IIIa receptor inhibitor such as abciximab, or a non-steroidal anti-inflammatory drug such as ibuprofen. Most preferably the platelet function altering agent is aspirin. Platelet function altering agents are categorised in the British
 5 National Formulary Section 2.9 and in other equivalent national formularies or pharmacopoeias. Non-steroidal anti-inflammatory drugs are categorised in the British National Formulary Section 10.1.1 and in other equivalent national formularies or pharmacopoeias. Preferably the aspirin is administered in an amount of from about 15 mg to about 500 mg per day; more preferably the aspirin is administered in an amount of from
 10 about 25 mg to about 250 mg per day; most preferably the aspirin is administered in an amount of about 75 mg per day.

Preferably the plasma/serum homocysteine lowering agent is folic acid, vitamin B6, or vitamin B12. Most preferably the plasma/serum homocysteine lowering agent is folic acid.
 15 Preferably the folic acid is administered in an amount of from about 0.2 mg to about 4 mg per day; more preferably the folic acid is administered in an amount of from about 0.4 mg to about 2 mg per day; most preferably the folic acid is administered in an amount of about 0.8 mg per day.

- 20 Most preferably the formulation comprises:
- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
 - ii) about 10 mg atorvastatin as lipid-regulating agent,
 - iii) about 75 mg aspirin as platelet function altering agent, and
 - 25 iv) about 0.8 mg folic acid as plasma/serum homocysteine lowering agent.

All preferred dosages are calculated to be at levels optimising the ratio of benefit to hazard, i.e. the ratio of reduction of the risk of cardiovascular disease to the risk of adverse effects of the administered agent.

30

Optionally the formulation of the present invention further comprises an active principal from a fifth category comprising anti-oxidants. Preferably the antioxidant is vitamin E.

The formulation of the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal (including patches), airway (aerosol), rectal and topical (including buccal and sublingual) administration. Preferably the formulation of the present invention is provided in a form suitable for oral
5 administration. For oral administration, the formulation of the present invention is preferably in the form of a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension.

Tablets for oral use may include the components mixed with pharmaceutically acceptable
10 excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally
15 be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the components are mixed
20 with a solid diluent, and soft gelatin capsules wherein the components are mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

The desired dose is preferably presented once daily, but may be dosed as two, three, four or more sub-doses administered at appropriate intervals throughout the day. Preferably the
25 active principals are present in the tablet, capsule, pill, powder, granules, a solution, or suspension in amounts suitable for administration once, twice, or three times per day. More preferably the active principals are present in the tablet, capsule, pill, powder, granules, a solution, or suspension in amounts suitable for administration once per day.

30 Preferably the formulation is used as a medicament. More preferably the formulation is used as a medicament for the prevention of cardiovascular disease. More preferably the formulation is used as a medicament for the prevention of ischaemic heart disease and stroke.

Preferably the formulation is used in men and women above a specified age for the reduction in the risk of cardiovascular disease. Alternatively the formulation is used in men and women with an estimated risk of cardiovascular disease above a specified level,
 5 wherein the risk is determined by measurement of risk factors used in conjunction with a person's age and sex. The formulation is also used in persons with a clinical history of coronary artery disease or cardiovascular disease irrespective of age or the values of risk factors.

10 Preferably the use of the formulation of the present invention reduces the risk of cardiovascular disease by at least 80%.

The present invention further provides the use of the formulation of the present invention for the manufacture of a medicament for the prevention of cardiovascular disease,
 15 preferably the manufacture of a medicament for the prevention of ischaemic heart disease or stroke. Preferably the medicament is used in men and women above a specified age for the reduction in the risk of cardiovascular disease. Preferably the medicament is used in men and women with an estimated risk of cardiovascular disease above a specified level, wherein the risk is determined by measurement of risk factors used in conjunction with a
 20 person's age and sex.

The present invention further provides a method of preparing the formulation of the present invention, comprising the steps of:

- 25 i) mixing the two or more active principals optionally with one or more pharmaceutically acceptable excipients, and
- ii) forming the mixture into a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension suitable for oral administration to a patient.

Figure 1 is a graph showing the relative risk (95% confidence limits) of stroke according to
 30 blood pressure (reference 1). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 2 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease (IHD) according to blood pressure (reference 1). Both vertical and horizontal axes are plotted on logarithmic scales.

- 5 Figure 3 is a graph showing the mortality (95% confidence limits) from ischaemic heart disease according to serum cholesterol (reference 2). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 4 is a graph showing the incidence (95% confidence limits) of ischaemic heart
10 disease according to plasma/serum homocysteine (reference 3). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 5 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease according to platelet aggregation (reference 4). The vertical axis is plotted on a
15 logarithmic scale.

For each of the factors that affect the risk of heart disease and stroke and that can be favourably altered by drug therapy (blood pressure, serum cholesterol, plasma/serum homocysteine and platelet function), the relationships with heart disease and stroke are
20 continuous across the range of values in Western populations. The higher the value of the risk factor, the greater is the risk of heart disease and stroke; an increased risk is not confined to persons with unusually high values of the risk factors. For each of the four risk factors, this continuous proportionate relationship has been established by two classes of evidence.

25

The first is a series of epidemiological studies in which measurements were made on a large number of persons and the values of the risk factors correlated against the subsequent incidence of heart attacks and stroke. Figures 1 to 5 show five sets of data on the relationships between cardiovascular risk factors and the incidence of ischaemic heart
30 disease or stroke (namely, blood pressure and stroke, blood pressure and ischaemic heart disease, serum cholesterol and ischaemic heart disease, plasma/serum homocysteine and ischaemic heart disease, body mass index and ischaemic heart disease). The data are either from single large epidemiological studies or from studies in which the data from several

smaller studies have been combined (references 1-4). The study populations have been divided into subgroups (five equal subgroups in three of the five relationships shown) according to ranked values of the risk factor, as shown on the horizontal axes. Incidence, on the vertical axes, is plotted on a logarithmic (or proportional) scale. In each case the relationship is well described by a straight line, and in Figures 1 to 4 the 95% confidence intervals on each of the estimates of incidence are inconsistent with a relationship that is markedly non-linear. The linear relationship indicates that given a change in one of the risk factors from any point on the distribution is associated with a constant proportionate change in the risk of heart disease and stroke.

10

The second class of evidence is randomised controlled trials in which medication was given to lower the risk factors. Randomised trials have shown that drugs that lower blood pressure produced the same proportionate reduction in the incidence of heart attacks and stroke, irrespective of whether the starting blood pressure was high or average (reference 5). Similarly, randomised trials have shown that drugs that lower serum cholesterol have produced the same proportionate reduction in the incidence of heart attacks and stroke, irrespective of whether the starting concentration of serum cholesterol was high or average (references 6-7). Randomised trials have shown that aspirin reduces the incidence of heart attacks and stroke in both high risk and low risk persons (reference 8) (platelet function was not measured in the aspirin trials). For plasma/serum homocysteine no randomised trials are yet available, but evidence is available on persons with different genetic disorders that increase homocysteine concentration to varying extents; the increase in risk of cardiovascular disease in the different disorders is commensurate with the increase in homocysteine (references 3, 9).

25

Because of this continuous proportionate relationship between each of these risk factors and the incidence of ischaemic heart disease and stroke, it would be appropriate to alter all four of them in a person whose risk is high for any reason - a particularly high blood pressure for example, some genetic predisposition (recognised or unrecognised), or simply increasing age. The decision that preventive treatment in an individual is worthwhile should be based on the person's overall level of risk of a heart attack or stroke, not on the level of a particular risk factor. Because of the constant proportionate relationship, the benefit will be greater in those whose risk is greater. The preferred approach therefore is

30

to use all these agents to lower risk in persons whose existing overall risk is above a specified level. There is a need for a treatment strategy and a formulation that will combine the benefits of all of them, while minimising the occurrence of adverse effects (thereby increasing the potency: hazard ratio), and for the formulation to be available on a
5 wide scale to individuals above a specified risk of having a major cardiovascular episode.

Despite the aetiological importance of the cardiovascular risk factors, their effectiveness in predicting risk in an individual is relatively weak (reference 10). A more important determinant of risk is age: the incidence of myocardial infarction and stroke doubles with
10 every eight years of advancing age. By contrast, a doubling of risk occurs over a wide span of the distributions of the four risk factors (references 3, 4, 11, 12) (approximately from the 5th centile of the distributions to the 50th, or from the 50th to the 95th). Sex is also an important determinant of risk - the incidence in women at any age is about the same as that in men ten years younger. However, the single most important determinant of
15 a person's risk is the presence of existing disease: in a person who has already had a heart attack or a stroke, for example, the risk of death from cardiovascular disease is about 5% per year, irrespective of age, sex, or the values of the risk factors.

The formulation of the present invention contains various components all designed to
20 reduce the risk of cardiovascular disease by changing different predisposing risk factors. The formulation is prepared in doses that maximise efficacy and minimise adverse effects. Preferably the formulation is offered to all persons above a certain age or risk cut-off. The start of treatment could be determined firstly by a person's history of existing disease: any person with a history of previous myocardial infarction or angina, or a previous stroke or
25 transient ischaemic attack, irrespective of age, sex, or the values of the risk factors, would be at sufficient risk to take the integrated formulation. In persons with no history of past disease, the start of treatment could be determined simply by a person's age and sex so that all men above a specified age (say 50 years) would take the integrated formulation each day and women could follow the same strategy but start at an older age (say at age 60
30 years). Alternatively, treatment could begin when a person's annual risk of ischaemic heart disease and stroke, calculated from their age, sex, and easily measurable risk factors (for example smoking, blood pressure and body mass index) was above a specified value. Such a policy would be substantially more effective than the current practice of using

pharmacological agents specific for a single risk factor and doing so only in individuals with high values of that risk factor or in individuals who have already suffered a major cardiovascular episode. The proposed new approach also takes into account, where current practice does not, that a history of previous cardiovascular disease and, in healthy persons, age are far more discriminatory measures of high risk than any of the cardiovascular risk factors.

Table 2 shows the risk factors altered by each of these drugs, the amount by which each one is changed on average by the preferred dosage, and the resulting expected reduction in the risks of ischaemic heart disease and stroke. Table 2 also shows that all the drugs in combination reduce the risk of ischaemic heart disease by an estimated 88% and of stroke by an estimated 86%. This combined estimate is based on the fact that the effects on the four different risk factors are unrelated and so the expected effects of changing each one will be independent of each other. This expectation is supported by two classes of evidence. First, epidemiological studies (in which the values of the risk factors were measured in many thousands of persons and the distribution of values examined in those who subsequently died of heart disease and stroke and those who did not) have shown that blood pressure, serum cholesterol, platelet function, and plasma/serum homocysteine are largely independent of each other in relation to the risk of cardiovascular disease (references 2, 3, 6, 218). For example the ratio of the risk of a disease event in persons with high blood pressure and the risk in persons with low blood pressure is similar, irrespective of the values of cholesterol and other risk factors. Second, some randomised clinical trials have used combinations of two of the drugs (for example beta blockers and aspirin) and have shown that the effects are independent (that is, the relative risk in patients who took two drugs (compared with the risk in those who took none) was similar to the relative risk in persons taking one of the drugs multiplied by the relative risk in persons taking the other drug). Accordingly, the effect of the different drugs in combination in Table 2 has been calculated by multiplying the effects of each as shown in footnotes h and j.

Drug	Example (daily dose)	Associated physiological variable (reduction produced by drug)	Expected reduction in risk of:	
			ischaemic heart disease	stroke
Thiazide diuretic	Hydrochlorothiazide (12.5 mg)	Blood pressure (12 mmHg diastolic) ^a	43% ^b	63% ^b
Beta blocker	Atenolol (25 mg)			
ACE inhibitor	Enalapril (5 mg)			
Statin	Atorvastatin (10 mg)	Serum cholesterol (1.8 mmol/l) ^c	61% ^d	50% ^d
Aspirin	Aspirin (75 mg)	Platelet aggregation	38% ^e	15% ^e
Folic acid	Folic acid (0.8 mg)	Plasma/serum homocysteine (3 µmol/l) ^f	15% ^g	10% ^g
All drugs in combination			88% ^h	86% ^j

Table 2 - The constituent drugs in the proposed combined formulation, the cardiovascular risk factors that each alter, the amount by which each factor would be changed, and the resulting expected reduction in risk of ischaemic heart disease and stroke.

5

^a Estimate obtained by us from an analysis of the blood pressure reduction according to dose in 187 randomised placebo controlled trials of thiazide or thiazide-like diuretics, beta-blockers and ACE inhibitors (references 13-199).

10 ^b Reduction in risk to be expected from the blood pressure reduction of 12 mmHg diastolic, from published analyses of cohort studies and randomised controlled trials of blood pressure and ischaemic heart disease and stroke (references 1,5).

^c From published randomised placebo controlled trials of atorvastatin (reference 200).

15 ^d The reduction in risk to be expected from the serum cholesterol reduction of 1.8 mmol/l, from published analyses of cohort studies and randomised controlled trials of serum cholesterol and ischaemic heart disease, and of randomised controlled trials of serum cholesterol reduction and stroke (references 6, 201, 202).

^e Estimate obtained by us from an analysis of the results of 14 randomised controlled trials of aspirin in dosage of 50-100 mg daily and the incidence of ischaemic heart disease and stroke (references 203-216).

20 ^f A meta-analysis of published randomised controlled trials of folic acid in doses between 1 mg and 5 mg showed that the maximum reduction in plasma homocysteine is 3 µmol/l and that this maximum reduction is produced by a folic acid dose of 1 mg (reference 217); an unpublished randomised controlled trial performed by us has suggested that a folic acid dose of 0.8 mg is the lowest dose that produces this maximum reduction in homocysteine.

25 ^g The reduction in risk to be expected from the reduction in plasma homocysteine of 3 µmol/l from the results of cohort studies of homocysteine and cardiovascular disease (references 3, 9).

^h $100\% - [(100\% - 43\%) \times (100\% - 61\%) \times (100\% - 38\%) \times (100\% - 15\%)] = 88\%.$

^j $100\% - [(100\% - 63\%) \times (100\% - 50\%) \times (100\% - 15\%) \times (100\% - 10\%)] = 86\%.$

30

Table 3 shows estimates of the prevalence of adverse effects from each of the medications when taken in the preferred dose. The dose of each medication has been chosen to maximise the ratio of benefit to hazard. It is recognised that some persons taking a combination of six drugs would develop adverse effects that were unacceptable. The adverse effects attributable to each of the component medications would be made clear to persons taking the combined formulation and alternative formulations omitting one or more of the component ingredients, with or without a substitute ingredient, would be available for persons unable to tolerate one component.

Drug	Example (daily dose)	Commonest adverse effects	Prevalence of any adverse effect in randomised trials (treated minus control)	Prevalence of serious adverse effects (those that warranted withdrawal from randomised trial)
Thiazide diuretic	Hydrochlorothiazide (12.5 mg)	dizziness, impotence, nausea	1.4% ^a	0.1% ^a
Beta blocker	Atenolol (25 mg)	cold extremities, fatigue, dizziness	5.6% ^a	0.9% ^a
ACE inhibitor	Enalapril (5 mg)	cough	2.1% ^a	0.2% ^a
Statin	Atorvastatin (10 mg)	-	0.1%	< 0.1%
Aspirin	Aspirin (75 mg)	bleeding, indigestion	1.8% ^b	0.7% ^b (mainly rectal or urinary bleeding)
Folic acid	Folic acid (0.8 mg)	-	< 0.1%	< 0.1%

Table 3 - The estimated prevalence of adverse effects of each of the six drugs to be included in the integrated formulation

^a Estimate obtained by us from an analysis of the prevalence of adverse effects according to dose in 187 randomised placebo controlled trials of thiazide diuretics, beta-blockers and ACE inhibitors (references 13-199).

^b Estimate obtained by us from an analysis of the prevalence of adverse effects in 14 randomised placebo controlled trials of aspirin in dosage between 50 and 100 mg (references 203-216).

The doses of the first three drugs listed in Tables 2 and 3 (the drugs used to lower blood pressure) are half the present standard (or recommended) dose. Table 4 shows the reduction in blood pressure and in the incidence of ischaemic heart disease and stroke, and

the prevalence of adverse effects, from using half standard dose (as in Tables 2 and 3) and from using the present standard (or recommended) dose. There is little loss of efficacy using half standard dose, but the prevalence of adverse effects is reduced by almost half. In other words, the ratio of benefit to hazard is greater. The preferred dose of aspirin is the

5 dose generally used in the prevention of cardiovascular disease (75 mg); this is much less than the dose necessary to relieve pain.

	Half standard dose (preferred dose)	Standard dose
Reduction in diastolic blood pressure	12 mmHg	15 mmHg
Proportionate reduction in incidence of:		
ischaemic heart disease	43%	50%
stroke	63%	71%
Prevalence of adverse effects	9%	16%

10 **Table 4** - The combined effect of three drugs that lower blood pressure (a thiazide diuretic, a beta blocker and an ACE inhibitor) in lowering blood pressure, and reducing the incidence of ischaemic heart disease and stroke, together with the combined prevalence of adverse effects, according to whether the drugs are given in half standard

dose or standard dose.

15 Estimates were obtained by us from an analysis of the blood pressure reduction and prevalence of adverse effects according to dose in 187 randomised placebo controlled trials of thiazide diuretics, beta-blockers and ACE inhibitors (references 13-199). The corresponding reductions in incidence of ischaemic heart disease and stroke are those to be expected from the blood pressure reductions, from published analyses of cohort studies and

20 randomised controlled trials of blood pressure and ischaemic heart disease and stroke (references 1, 5).

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various

25 modifications and embodiments can be made without departing from the scope of the invention, which is defined by the following claims only.

References:

1. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;**335**:765-74
2. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. *Arch Intern Med* 1992;**152**:56-64
3. Wald NJ, Watt HC, Law MR, Weir DG, McPartlin J, Scott JM. Homocysteine and ischaemic heart disease: results of a prospective study with implications on prevention. *Arch Intern Med* 1997
4. Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ* 1997;**315**:973-88
5. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;**335**:827-38
6. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;**308**:367-72
7. Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995;**345**:1274-5
8. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81-106
9. Law MR. Lowering heart disease risk with cholesterol reduction: evidence from observational studies and clinical trials. *European Heart Journal Supplements* 1999; 1 (Suppl S): S3-S8
10. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ* 1999;**319**:1562-5
11. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. *Arch Intern Med* 1993;**153**:598-615

12. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? *JAMA* 1986;256:2823-8
13. Petersen JR, Draback H, Gleeurup G, Mehlsen J, Petersen LJ, Winther K. ACE Inhibition with spirapril improves diastolic function at rest independent of vasodilation during treatment with spirapril in mild to moderate hypertension. *Angiology* 1996;47:233-40
14. Burris JF, Weir MR, Oparil S, Weber M, Cady WJ, Stewart WH. An assessment of diltiazem and hydrochlorothiazide in hypertension. *JAMA* 1990;263:1507-12
15. Scholze J, Breitstadt A, Cairns V, Bauer B, Bender N, Priestley, et al. Ramipril and hydrochlorothiazide combination therapy in hypertension: a clinical trial of factorial design. *J Hypertens* 1993;11:217-21
16. Frei M, Küster L, von Krosigk PG, Koch H, Küppers. Moxonidine and hydrochlorothiazide in combination: a synergistic antihypertensive effect. *J Cardiovasc Pharmacol* 1994;24(Suppl 1):S25-S28
17. Goldberg MR, Rockhold FW, Offen WW, Dornseif BE. Dose-effect and concentration-effect relationships of pinacidil and hydrochlorothiazide in hypertension. *Clin Pharmacol Ther* 1989;46:208-18
18. Muiesan G, Agabiti-Rosei E, Buoninconti R, Cagli V, Carotti A, Corea L, et al. Antihypertensive efficacy and tolerability of captopril in the elderly: comparison with hydrochlorothiazide and placebo in a multicentre, double-blind study. *J Hypertens* 1987;5 (Suppl 5):S599-S602
19. Pool PE, Applegate WB, Woehler T, Sandall P, Cady WJ. A randomized, controlled trial comparing diltiazem, hydrochlorothiazide, and their combination in the therapy of essential hypertension. *Pharmacotherapy* 1993;13:487-93
20. Wing LMH, Arnold LF, Harvey PJ, Upton J, Molloy D, Bune AJC, et al. Lacidipine, hydrochlorothiazide and their combination in systolic hypertension in the elderly. *J Hypertens* 1997;15:1503-10
21. Chalmers JP, Morris MJ, Wing LMH, Cain MD, West MJ, Graham JR, et al. Effects of enalapril and hydrochlorothiazide on blood pressure, renin-angiotensin system, and atrial natriuretic factor in essential hypertension: a double blind factorial cross-over study. *Aust NZ J Med* 1986;16:475-80
22. Chalmers JP, Korner PI, Tiller DJ, Bune AJ, Steiner JD, West MJ, et al. Double-

- blind factorial trial of prindolol and hydrochlorothiazide in hypertension. *Med J Aust* 1976;1:650-3
23. Chalmers J, Horvath J, Tiller D, Bune A. Effects of timolol and hydrochlorothiazide on blood-pressure and plasma renin activity. *Lancet* 1976;2:328-31
 24. McCorvey E, Wright JT, Culbert JP, McKenney JM, Proctor JD, Annett MP. Effect of hydrochlorothiazide, enalapril, and propranolol on quality of life and cognitive and motor function in hypertensive patients. *Clinical Pharmacy* 1993;12:300-5
 25. Myers MG, de Champlain J. Effects of atenolol and hydrochlorothiazide on blood pressure and plasma catecholamines in essential hypertension. *Hypertension* 1983;5:591-6
 26. Jounela AJ, Lilja M, Lumme J, Mörlin C, Hoyem A, Wessel-aas T, et al. Relation between low dose of hydrochlorothiazide, antihypertensive effect and adverse effects. *Blood Press* 1994;3:231-5
 27. Pool J, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. *Am J Hypertens* 1997;10:117-23
 28. Canter D, Frank GJ, Knapp LE, Phelps M, Quade M, Texter M. Quinapril and hydrochlorothiazide combination for control of hypertension: assessment by factorial design. *J Hum Hypertens* 1994;8:155-62
 29. Frishman WH, Bryzinski BS, Coulson LR, DeQuattro VL, Vlachakis ND, Mroczek WJ, et al. A multifactorial trial design to assess combination therapy in hypertension. *Arch Intern Med* 1994;154:1461-9
 30. Zachariah PK, Messerli FH, Mroczek W. Low-dose bisoprolol/hydrochlorothiazide: an option in first-line, antihypertensive treatment. *Clin Ther* 1993;15:779-87
 31. Chrysant SG. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination. *Arch Intern Med* 1994;154:737-43
 32. Fernández M, Madero R, González D, Camacho P, Villalpando J, Arriaga J. Combined versus single effect of fosinopril and hydrochlorothiazide in hypertensive patients. *Hypertension* 1994;23 (Suppl I):I-207-10

33. Lacourcière Y, Arnott W. Placebo-controlled comparison of the effects of nebivolol and low-dose hydrochlorothiazide as monotherapies and in combination on blood pressure and lipid profile in hypertensive patients. *J Hum Hypertens* 1994;8:283-8
34. Pordy RC. Cilazapril plus hydrochlorothiazide: improved efficacy without reduced safety in mild to moderate hypertension. *Cardiology* 1994;85:311-22
35. Weir MR, Weber MA, Punzi HA, Serfer HM, Rosenblatt S, Cady WJ. A dose escalation trial comparing the combination of diltiazem SR and hydrochlorothiazide with the monotherapies in patients with essential hypertension. *J Hum Hypertens* 1992;6:133-8
36. Brown CL, Backhouse CI, Grippat JC, Santoni JP. The effect of perindopril and hydrochlorothiazide alone and in combination on blood pressure and on the renin-angiotensin system in hypertensive subjects. *Eur J Clin Pharmacol* 1990;39:327-32
37. Chrysant SG, Fagan T, Glazer R, Kriegman A. Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension. *Arch Fam Med* 1996;5:17-24
38. Frishman WH, Burris JF, Mroczek WJ, Weir MR, Alemayehu D, Simon JS, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol* 1995;35:182-8
39. Kayanakis JG, Baulac L. Comparative study of once-daily administration of captopril 50mg, hydrochlorothiazide 25mg and their combination in mild to moderate hypertension. *Br J Clin Pharmacol* 1987;23 (Suppl 1):89S-92S
40. Moser M, Abraham PA, Bennett WM, Brachfeld N, Goodman RP, McKenney JM, et al. The effects of benazepril, a new angiotensin-converting enzyme inhibitor, in mild to moderate essential hypertension: a multicenter study. *Clin Pharmacol Ther* 1991;49:322-9
41. Persson B, Stimpel M. Evaluation of the antihypertensive efficacy and tolerability of moexipril, an new ACE inhibitor, compared to hydrochlorothiazide in elderly patients. *Eur J Clin Pharmacol* 1996;50:259-64
42. Jueng C, Halperin AK, Hasmimoto F, Callender K. Nifedipine GITS and hydrochlorothiazide in essential hypertension. *J Clin Hypertens* 1987;3:695-703

43. Scholz D, Schwille PO, Sigel A. Double-blind study with thiazide in recurrent calcium lithiasis. *J Urol* 1982;128:903-7
44. Materson BJ, Oster JR, Michael UF, Bolton SM, Burton ZC, Stambaugh JE, et al. Dose response to chlorthalidone in patients with mild hypertension. *Clin Pharmacol Ther* 1978;24:192-8
45. Morledge JH, Ettinger B, Aranda J, BcBarron F, Barra P, Gorwit J, et al. Isolated systolic hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. *J Am Geriatr Soc* 1986;34:199-206
46. Bateman DN, Dean CR, Mucklow JC, Bulpitt CJ, Dollery CT. Atenolol and chlorthalidone in combination for hypertension. *Br J Clin Pharmacol* 1979;7:357-63
47. Erwtelman TM, Nagelkerke N, Lubsen J, Koster M, Dunning AJ. β Blockade, diuretics, and salt restriction for the management of mild hypertension: a randomised double blind trial. *BMJ* 1984;289:406-9
48. Ferrara LA, de Simone G, Mancini M, Fasano ML, Pasanisi F, Vallone G. Changes in left ventricular mass during a double-blind study with chlorthalidone and slow-release nifedipine. *Eur J Clin Pharmacol* 1984;27:525-8
49. McFate Smith WM, Feigal DW, Furberg CD, Greenlick M, Kuller L, Perry HM, et al. Use of diuretics in treatment of hypertension in the elderly. *Drugs* 1986;31:154-64
50. Moser M. Low-dose diuretic therapy for hypertension. *Clin Ther* 1986;8:554-62
51. Salvetti A, Magagna A, Innocenti P, Ponzanelli F, Cagianelli A, Cipriani M, et al. The combination of chlorthalidone with nifedipine does not exert an additive antihypertensive effect in essential hypertensives: a crossover multicenter study. *J Cardiovasc Pharmacol* 1991;17:332-5
52. Wing LMH, West MJ, Graham JR, Chalmers JP. Long-acting and short-acting diuretics in mild essential hypertension. *Clin Exp Hypertens* 1982;A4:1429-41
53. Bradley K, Flack JM, Belcher J, Elmer P, Miller P, Grimm R. Chlorthalidone attenuates the reduction in total cholesterol and small, dense LDL cholesterol subclass associated with weight loss. *Am J Hypertens* 1993;6:636-9
54. Cranston WI, Juel-Jensen BE. The effects of spironolactone and chlorthalidone on arterial pressure. *Lancet* 1962;1:1161-4
55. Durel LA, Hayashi PJ, Weidler DJ, Schneiderman N. Effectiveness of

- antihypertensive medications in office and ambulatory settings: a placebo-controlled comparison of atenolol, metoprolol, chlorthalidone, verapamil, and an atenolol-chlorthalidone combination. *J Clin Pharmacol* 1992;**32**:564-70
56. Hall WD, Weber MA, Ferdinand K, Flamenbaum W, Marbury T, Jain AK, et al. Lower dose diuretic therapy in the treatment of patients with mild to moderate hypertension. *J Hum Hypertens* 1994;**8**:571-5
 57. Fiddes R, Blumenthal J, Dawson JE, Dyckman E, Hammond PGS, Harris S, et al. Evaluation of indapamide 1.25mg once daily in elderly patients with mild to moderate hypertension. *J Hum Hypertens* 1997;**11**:239-44
 58. Weidler D, Jallad NS, Curry C, Ferdinand K, Jain AK, Schnaper HW, et al. Efficacious response with lower dose indapamide therapy in the treatment of elderly patients with mild to moderate hypertension. *J Clin Pharmacol* 1995;**35**:45-51
 59. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol* 1993;**22** (Suppl 6):S78-S86
 60. Chalmers JP, Wing LMH, Grygiel JJ, West MJ, Graham JR, Bune AJ. Effects of once daily indapamide and pindolol on blood pressure, plasma aldosterone concentration and plasma renin activity in a general practice setting. *Eur J Clin Pharmacol* 1982;**22**:191-6
 61. Schaller M, Waeber B, Brunner HR. Double-blind comparison of indapamide with a placebo in hypertensive patients treated by practicing physicians. *Clin Exp Hypertens* 1985;**A7**:985-94
 62. Taylor DR, Constable J, Sonnekus M, Milne FJ. Effect of indapamide on serum and red cell cations, with and without magnesium supplementation, in subjects with mild hypertension. *S Afr Med J* 1988;**74**:272-6
 63. Carlsen JE, Køber L, Torp-Pedersen, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990;**300**:975-8
 64. Christiansen C, Christensen MS, Hagen C, Stocklund KE, Transbøl. Effects of natural estrogen/gestagen and thiazide on coronary risk factors in normal postmenopausal women. *Acta Obstet Gynecol Scand* 1981;**60**:407-412
 65. Horvath JS, Caterson RJ, Collett P, Duggin GG, Kelly DH, Tiller DJ. Labetalol

- and bendrofluazide: comparison of their antihypertensive effects. *Med J Aust* 1979;1:626-8
66. Webster J, Dollery CT, Hensby CN. Circulating prostacyclin concentrations may be increased by bendrofluazide in patients with essential hypertension. *Clin Sci* 1980;59 (Suppl 6):125s-128s
 67. Wilcox RG. Randomised study of six beta-blockers and a thiazide diuretic in essential hypertension. *BMJ* 1978;2:383-5
 68. Fernandez PG, Zachariah PK, Bryant DG, Missan SS. Antihypertensive efficacy of α -methyldopa, chlorothiazide and Supres-150 (α -methyldopa-chlorothiazide). *Can Med Assoc J* 1980;123:284-7
 69. Curry CL, Harris R, MacKay JH, Nugent CA, Ryan J, Schnaper, et al. Clinical studies of a new, low-dose formulation of metolazone for the treatment of hypertension. *Clin Ther* 1986;9:47-62
 70. McVeigh G, Galloway D, Johnston D. The case for low dose diuretics in hypertension: comparison of low and conventional doses of cyclopenthiazide. *BMJ* 1988;297:95-8
 71. Chrysant SG, Chappel C, Farnham J, Levin B, Lueg M, McCluskey D, et al. Antihypertensive and metabolic effects of single and combined atenolol regimens. *J Clin Pharmacol* 1992;32:61-65
 72. Ekblom T, Dahlöf B, Hansson L, Lindholm LH, Scherstén B, Wester P. Antihypertensive efficacy and side effects of three beta-blockers and a diuretic in elderly hypertensives: a report from the STOP-Hypertension study. *J Hypertens* 1991;10:1525-9
 73. Gostick NK, Mayhew SR, Million R, Sagar D, Suxena SR, Igram DF, et al. A dose-response study of atenolol in mild to moderate hypertension in general practice. *Curr Med Res Opin* 1977;5:179-84
 74. Saul P, Jones BP, Edwards KG, Tweed JA. Randomized comparison of atenolol and placebo in the treatment of anxiety: a double-blind study. *Eur J Clin Pharmacol* 1985;28:109-110
 75. Tonkin AL, Wing LMH, Russell AE, West MJ, Bune AJC, Morris MJ, et al. Diltiazem and atenolol in essential hypertension: additivity of effects on blood pressure and cardiac conduction with combination therapy. *J Hypertens* 1990;8:1015-8

76. Wing LMH, Chalmers JP, West MJ, Russell AE, Morris MJ, Cain MD. Enalapril and atenolol in essential hypertension: attenuation of hypertensive effects in combination. *Clin Exp Hypertens* 1988;**10**:119-33
77. Cilliers AJ. Atenolol as primary therapy in previously untreated hypertensives and as an adjuvant to other therapy. *S Afr Med J* 1979;**55**:321-4
78. Clement DL, De Pue NY, Packet L. Effect of calcium antagonists on ambulatory blood pressure and its variations. *J Cardiovasc Pharmacol* 1987;**10** (Suppl 10):S117-S119
79. Houston MC, Burger C, Hays JT, Nadeau J, Swift L, Bradley CA, et al. The effects of clonidine hydrochloride versus atenolol monotherapy on serum lipids, lipid subfractions, and apolipoproteins in mild hypertension. *Am Heart J* 1990;**120**:172-9
80. Lange-Andersen KL, Ottmann W, Piatkowski W, Green KA. Working ability and exercise tolerance during treatment of mild hypertension. *Int Arch Occup Environ Health* 1985;**56**:49-55
81. Lyons D, Fowler G, Webster J, Hall ST, Petrie JC. An assessment of lacidipine and atenolol in mild to moderate hypertension. *Br J Clin Pharmacol* 1994;**37**:45-51
82. Streufert S, DePadova A, McGlynn T, Pogash R, Piasecki M. Impact of β -blockade on complex cognitive functioning. *Am Heart J* 1988;**116**:311-4
83. Tötterman K, Groop L, Groop P, Kala R, Tolppanen, Fyhrquist F. Effect of beta-blocking drugs on beta-cell function and insulin sensitivity in hypertensive non-diabetic patients. *Eur J Clin Pharmacol* 1984;**26**:13-7
84. Vanhees L, Fagard R, Lijnen P, Amery A. Effect of antihypertensive medication on endurance exercise capacity in hypertensive sportsmen. *J Hypertens* 1991;**9**:1063-8
85. Verdecchia P, Gatteschi C, Benemio G, Boldrini F, Guerrieri M, Porcellati C. Duration of the antihypertensive action of atenolol, enalapril and placebo. *Int J Clin Pharmacol Ther Toxicol* 1988;**26**:570-4
86. Clement DL, Bogaert MG, Pannier R. Effect of beta-adrenergic blockage on blood pressure variation in patients with moderate hypertension. *Eur J Clin Pharmacol* 1977;**11**:325-7
87. Baez MA, Garg DC, Jallad NS, Weidler DJ. Antihypertensive effect of doxazosin

- in hypertensive patients: comparison with atenolol. *Br J Clin Pharmacol* 1986;21 (Suppl 1):63S-67S
88. Jeffers TA, Webster J, Petrie JC. Atenolol once-daily in hypertension. *Br J Clin Pharmacol* 1977;4:523-7
 89. Maclean D, Mitchell ET, Lewis R, Irvine N, McLay S, McEwen J, et al. Comparison of once daily atenolol, nitrendipine and their combination in mild to moderate essential hypertension. *Br J Clin Pharmacol* 1990;29:455-63
 90. Van Nueten L, Taylor FR, Robertson JIS. Nebivolol vs atenolol and placebo in essential hypertension: a double-blind randomised trial. *J Hum Hypertens* 1998;12:135-40
 91. Petrie C, Jeffers TA, Robb OJ, Scott AK, Webster J. Atenolol, sustained-release oxprenolol, and long-acting propranolol in hypertension. *BMJ* 1980;1:1573-4
 92. Wilcox RG, Hampton JR. Comparative study of atenolol, metoprolol, metoprolol durules, and slow-release oxprenolol in essential hypertension. *Br Heart J* 1981;46:498-502
 93. Roberts DH, Tsao Y, McLoughlin GA, Breckenridge A. Placebo-controlled comparison of captopril, atenolol, labetalol, and pindolol in hypertension complicated by intermittent claudication. *Lancet* 1987;2:650-3
 94. Hansson L, Åberg H, Karlberg BE, Westerlund A. Controlled study of atenolol in treatment of hypertension. *BMJ* 1975;2:367-70
 95. Broekman CPM, Haensel SM, Ven de Ven LLM, Slob AK. Bisoprolol and hypertension: effects on sexual functioning in men. *J Sex Marital Ther* 1992;18:325-31
 96. Davidov ME, Singh SP, Vlachakis ND, Blumenthal JB, Simon JS, Bryzinski JS, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. *Clin Cardiol* 1994;17:263-268
 97. Tseng C, Chiang F, Hsu K, Tseng Y, Hu W, Chen J, et al. Short-term efficacy and safety of bisoprolol in treatment of patients with mild-to-moderate hypertension - A two-center, double-blind study in Taiwan. *Acta Cardiologica Sinica* 1993;9:155-60
 98. Van de Ven LLM, Mouthaan BJ, Hoes MJ. Treatment of hyperventilation syndrome with bisoprolol: a placebo-controlled clinical trial. *J Psychosom Res* 1995;39:1007-13

99. Asmar RG, Kerihuel JC, Girerd XJ, Safar ME. Effect of bisoprolol on blood pressure and arterial hemodynamics in systemic hypertension. *Am J Cardiol* 1991;68:61-4
100. Ameling EH, de Korte DF, Man in 't Veld AJ. Impact of diagnosis and treatment of hypertension on quality of life: a double-blind, randomized, placebo-controlled, cross-over study of betaxolol. *J Cardiovasc Pharmacol* 1991;18:752-60
101. Williams RL, Goyle KK, Herman TS, Rofman BA, Ruoff GE, Hogan LB. Dose-dependent effects of betaxolol in hypertension: a double-blind multicenter study. *J Clin Pharmacol* 1992;32:360-7
102. Salonen JT, Palminteri R. Comparison of two doses of betaxolol and placebo in hypertension: a randomised, double-blind cross-over trial. *Eur J Clin Pharmacol* 1982;23:491-4
103. Jäättelä A, Baandrup S, Houtzagers J, Westergren G. The efficacy of low dose metoprolol CR/ZOK in mild hypertension and in elderly patients with mild to moderate hypertension. *J Clin Pharmacol* 1990;30 (Suppl):S66-S71
104. Landin K, Tengborn L, Smith U. Metformin and metoprolol CR treatment in non-obese men. *J Intern Med* 1994;235:335-41
105. Groop L, Tötterman KJ, Harno K, Gordin A. Influence of beta-blocking drugs on glucose metabolism in hypertensive, non-diabetic patients. *Acta Med Scand* 1983;213:9-14
106. Lepäntalo MJA, Tötterman KJ. Lower limb haemodynamics during antihypertensive treatment with metoprolol and propranolol. *Inter Angiol* 1985;4:225-8
107. MacMahon S, MacDonald GJ, Bernstein L, Andrews G, Blacket RB. Comparison of weight reduction with metoprolol in treatment of hypertension in young overweight patients. *Lancet* 1985;1:1233-6
108. Reybrouck T, Amery A, Fagard R, Jousten P, Lijnen P, Meulepas E. Beta-blockers: once or three times a day? *BMJ* 1978;1:1386-8
109. Vandongen R, Margetts B, Deklerk N, Beilin LJ, Rogers P. Plasma catecholamines following exercise in hypertensives treated with pindolol: comparison with placebo and metoprolol. *Br J Clin Pharmacol* 1986;21:627-32
110. Trafford JAP, Latta D, Little PS, Parsley J, Ankier SI. A multi-centre, placebo controlled comparative study between 200 mg and 400 mg celiprolol in patients

- with mild to moderate essential hypertension. *Curr Med Res Opin* 1989;11:550-6
111. Kimura S, DeQuattro V, Hernandez PH, Lee DD. Effects of celiprolol on plasma renin, aldosterone, norepinephrine and epinephrine in primary hypertension. *Am J Cardiol* 1988;62:751-4
 112. Watson RDS, Stallard TJ, Littler WA. Comparison of once and twice daily administration of acebutolol in hypertension. *Br J Clin Pharmacol* 1980;9:209-12
 113. Van Nueten L, Dupont AG, Vertommen C, Goyvaerts H, Robertson JIS. A dose-response trial of nebivolol in essential hypertension. *J Hum Hypertens* 1997;11:139-44
 114. Himmelmann A, Hedner T, Snoeck E, Lundgren B, Hedner J. Haemodynamic effects and pharmacokinetics of oral *d*- and *l*-nebivolol in hypertensive patients. *Eur J Clin Pharmacol* 1996;51:259-64
 115. Glasscock RJ, Weitzman RE, Bennett CM, Maxwell M, Hamilton B, Winer N, et al. Pindolol: effects on blood pressure and plasma renin activity. *Am Heart J* 1982;104:421-5
 116. Hamilton BP, Hamilton J, Kirkendall WM. Pulmonary function in hypertensive patients treated with pindolol: a report of two studies. *Am Heart J* 1982;104:432-7
 117. Galloway DB, Glover SC, Hendry WG, Logie AW, Petrie JC, Smith MC, et al. Propranolol in hypertension: a dose-response study. *BMJ* 1976;2:140-2
 118. Dargie H, Cleland J, Findlay I, Murray G, McInnes G. Combination of verapamil and beta-blockers in systemic hypertension. *Am J Cardiol* 1986;57:80D-82D
 119. McInnes GT, Findlay IN, Murray G, Cleland JGF, Dargie HJ. Cardiovascular responses to verapamil and propranolol in hypertensive patients. *J Hypertens* 1985;3 (Suppl 3):S219-21
 120. Hudson CFE. An evaluation of once daily long acting propranolol hydrochloride (Inderal LA and Half-Inderal LA) in the treatment of anxiety. A double-blind placebo-controlled general practice study. *Br J Clin Pract* 1988;42:419-26
 121. Pearson RM, Bulpitt CJ, Havard CWH. Biochemical and haematological changes induced by tienilic acid combined with propranolol in essential hypertension. *Lancet* 1979;1:697-9
 122. Moleur P, Peyrieux JC, Luciani J, David D, Boissel JP. Bopindolol in the treatment of moderate hypertension: a dose-response study. *Fundam Clin Pharmacol* 1988;2:431-40

123. Adsett CA, Bellissimo A, Mitchell A, Wilczynski N, Haynes RB. Behavioral and physiological effects of a beta-blocker and relaxation therapy on mild hypertensives. *Psychosom Med* 1989;**51**:523-6
124. Dupont AG, Vanderniepen P, Bossuyt AM, Jonckheer MH, Six RO. Nadolol in essential hypertension: effect on ambulatory blood pressure, renal haemodynamics and cardiac function. *Br J Clin Pharmacol* 1985;**20**:93-99
125. Casadei B, Conway J, Coats AJS, Bird R. Antihypertensive effect of carvedilol: a preliminary dose-response study. *Clinical Investigator* 1992;**70** (Suppl):S37-S38
126. Dupont AG, Van der Niepen P, Taeymans Y, Ingels M, Piepsz A, Bossuyt AM, et al. Effect of carvedilol on ambulatory blood pressure, renal hemodynamics, and cardiac function in essential hypertension. *J Cardiovasc Pharmacol* 1987;**10** (Suppl 11):S130-S136
127. Morgan TO, Morgan O, Anderson A. Effect of dose on trough peak ratio of antihypertensive drugs in elderly hypertensive males. *Clin Exp Pharmacol Physiol* 1995;**22**:778-80
128. Chrysant SG, Brown RD, Kem DC, Brown JL. Antihypertensive and metabolic effects of a new converting enzyme inhibitor, enalapril. *Clin Pharmacol Ther* 1983;**33**:741-6
129. Kaski JC, Rosano G, Gavrielides S, Chen L. Effects of angiotensin-converting enzyme inhibition on exercise induced angina and ST segment depression in patients with microvascular angina. *J Am Coll Cardiol* 1987;**23**:652-7
130. Küppers HE, Jäger BA, Lusztick JH, Gräve, Hughes PR, Kaan EC. Placebo-controlled comparison of the efficacy and tolerability of once-daily moxonidine and enalapril in mild-to-moderate essential hypertension. *J Hypertens* 1997;**15**:93-7
131. Naranjo CA, Kadlec KE, Sanhueza P, Woodley-Remus D, Sellers EM. Enalapril effects on alcohol intake and other consummatory behaviors in alcoholics. *Clin Pharmacol Ther* 1991;**50**:96-106
132. Simon G, Morioka S, Snyder DK, Cohn JN. Increased renal plasma flow in long-term enalapril treatment of hypertension. *Clin Pharmacol Ther* 1983;**34**:459-65
133. van Baak MA, Mooij JMV, Wijnen JAG, Tan FS. Submaximal endurance exercise performance during enalapril treatment in patients with essential hypertension. *Clin Pharmacol Ther* 1991;**50**:221-7

134. Whelton A, Dunne B, Glazer N, Kostis JB, Miller WE, Rector DJ, et al. Twenty-four hour blood pressure effect of once-daily lisinopril, enalapril, and placebo in patients with mild to moderate hypertension. *J Hum Hypertens* 1992;6:325-31
135. Gibbs JSR, Crean PA, Mockus L, Wright C, Sutton G, Fox KM. The variable effects of angiotensin converting enzyme inhibition on myocardial ischaemia in chronic stable angina. *Br Heart J* 1989;62:112-7
136. Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snavely DB, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension* 1995;25:1345-50
137. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Eng J Med* 1998;338:784-90
138. Forette F, Handfield-Jones R, Henry-Amar M, Fouchard M, Bouchacourt P, Hervy M, et al. Rationale for ACE inhibition in the elderly: treatment of arterial hypertension with enalapril. *Gerontology* 1987;33:9-16
139. Sassano P, Chatellier G, Alhenc-Gelas F, Corvol P, Menard J. Antihypertensive effect of enalapril as first-step treatment of mild and moderate uncomplicated essential hypertension. *Am J Med* 1984;77(suppl 2A):18-22
140. Applegate WB, Cohen JD, Wolfson P, Davis A, Green S. Evaluation of blood pressure response to the combination of enalapril (single dose) and diltiazem ER (four different doses) in systemic hypertension. *Am J Cardiol* 1996;78:51-5
141. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. *Am J Hypertens* 1998;11:23-30
142. Franke H. Antihypertensive effects of candesartan cilexetil, enalapril and placebo. *J Hum Hypertens* 1997;11 (Suppl 2):S61-62
143. Levine JH, Ferdinand KC, Cargo P, Laine H, Lefkowitz M. Additive effects of verapamil and enalapril in the treatment of mild to moderate hypertension. *Am J Hypertens* 1995;8:494-9
144. Salvetti A, Arzilli F. Chronic dose-response curve of enalapril in essential hypertensives. *Am J Hypertens* 1989;2:352-4

145. Holwerda NJ, Fogari R, Angeli P, Porcellati C, Hereng C, Oddou-Stock P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J Hypertens* 1996;14:1147-51
146. Bergstrand R, Herlitz H, Johansson S, Berglund G, Vedin A, Wilhelmsson C, et al. Effective dose range of enalapril in mild to moderate essential hypertension. *Br J Clin Pharmacol* 1985;19:605-11
147. Louis WJ, Workman BS, Conway EL, Worland P, Rowley K, Drummer O, et al. Single-dose and steady-state pharmacokinetics and pharmacodynamics of perindopril in hypertensive subjects. *J Cardiovasc Pharmacol* 1992;20:505-11
148. Luccioni R, Frances Y, Gass R, Gilgenkrantz JM. Evaluation of the dose-effect relationship of perindopril in the treatment of hypertension. *Clin Exp Hypertens* 1989;A11:521-34
149. Myers MG. A dose-response study of perindopril in hypertension: effects on blood pressure 6 and 24h after dosing. *Am J Cardiol* 1996;12:1191-6
150. West JNW, Smith SA, Stallard TJ, Littler WA. Effects of perindopril on ambulatory intra-aarterial blood pressure, cardiovascular reflexes and forearm blood flow in essential hypertension. *J Hypertens* 1989;7:97-104
151. Chrysant SG, McDonald RH, Wright JT, Barden PL, Weiss RJ. Perindopril as monotherapy in hypertension: a multicenter comparison of two dosing regimens. *Clin Pharmacol Ther* 1993;53:479-84
152. Overlack A, Adamczak M, Bachmann W, Bönner G, Bretzel RG, Derichs R, et al. ACE-inhibition with perindopril in essential hypertensive patients with concomitant diseases. *Am J Med* 1994;97:126-34
153. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Low-dose captopril for the treatment of mild to moderate hypertension. *Arch Intern Med* 1984;144:1947-53
154. Drayer JIM, Weber MA. Monotherapy of essential hypertension with a converting-enzyme inhibitor. *Hypertens* 1983;5 (Suppl III):III108-13
155. Schoenberger JA, Wilson DJ. Once-daily treatment of essential hypertension with captopril. *J Clin Hypertens* 1986;4:379-87
156. Conway J, Way B, Boon N, Somers V. Is the antihypertensive effect of captopril influenced by the dosage frequency? A study with ambulatory monitoring. *J Hum*

- Hypertens* 1988;2:123-6
157. Lavessaro G, Ladetto PE, Valente M, Stramignoni D, Zanna C, Assogna G, et al. Ketanserin and captopril interaction in the treatment of essential hypertensives. *Cardiovasc Drugs Ther* 1990;4:119-22
 158. Salvetti A, Innocenti PF, Iardella M, Pambianco F, Saba GC, Rossetti M, et al. Captopril and nifedipine interactions in the treatment of essential hypertensives: a crossover study. *J Hypertens* 1987;5 (Suppl 4):S139-S142
 159. Salvetti A, Circo A, Raciti S, Gulizia M, Cardillo R, Miceli S, et al. Captopril at 50mg as well as at 100mg once a day reduces blood pressure for up to 24h: a double-blind randomized crossover study in mild to moderate hypertensives. *J Hypertens* 1988;6 (Suppl 4):S666-S668
 160. Fernandez PG, Bolli P, Lee C. The 24h blood pressure responses of hypertensives to a once-a-day cilazapril regimen. *Can J Cardiol* 1990;6:53-8
 161. Güntzel P, Kobrin I, Pasquier C, Zimlichman R, Viskoper JR. The effect of cilazapril, a new angiotensin converting enzyme inhibitor, on peak and trough blood pressure measurements in hypertensive patients. *J Cardiovasc Pharmacol* 1991;17:8-12
 162. Kobrin I, Güntzel P, Viskoper R, Paran E, Zimlichman R. Antihypertensive duration of action of cilazapril in patients with mild to moderate essential hypertension. *Drugs* 1991;41:31-6
 163. Krum H, Jackson B, Conway EL, Howes LG, Johnston CI, Louis WJ. Steady-state pharmacokinetics and pharmacodynamics of cilazapril in the presence and absence of cyclopenthiazide. *J Cardiovasc Pharmacol* 1992;20:451-7
 164. Lacourcière Y, Leenen F, Rangno R, Spence JD, Lenis JH, Myers MG. Discrepancies between clinic and ambulatory blood pressure responses to cilazapril therapy. *Can J Cardiol* 1994;10:605-10
 165. Mroczek WJ, Klein J, Burris JF. Dose-finding study of cilazapril (inhibace) in patients with uncomplicated essential hypertension. *Clin Exp Hypertens* 1991;A13:1415-32
 166. Prager G, Klein P, Schmitt M, Prager R. Antihypertensive efficacy of cilazapril 2.5 and 5.0mg once-daily versus placebo on office blood pressure and 24-hour blood pressure profile. *J Cardiovasc Pharmacol* 1994;24 (Suppl 3):S93-S99
 167. White WB, McCabe EJ, Hager WD, Schulman P. The effects of the long-acting

- angiotensin-converting enzyme inhibitor cilazapril on casual, exercise and ambulatory blood pressure. *Clin Pharmacol Ther* 1988;**44** (Suppl 3):173-8
168. Poirier L, Pyzyk M, Provencher P, Lacourcière. Comparative effects of 2.5 and 5mg cilazapril versus placebo on daily blood pressure load. *Am J Hypertens* 1991;**4**:913-5
 169. DeQuattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. *Am J Hypertens* 1997;**10** (Suppl):138S-145S
 170. Veratran Study Group. Effects of verapamil SR, trandolapril, and their fixed combination on 24-h blood pressure. *Am J Hypertens* 1997;**10**:492-9
 171. Weir MR, Gray JM, Paster R, Saunders E. Differing mechanisms of action of angiotensin-converting enzyme inhibition in black and white hypertensive patients. *Hypertension* 1995;**26**:124-30
 172. Mancina G, De Cesaris R, Fogari R, Lattuada S, Montemurro G, Palombo C, et al. Evaluation of the antihypertensive effect of once-a-day trandolapril by 24-hour ambulatory blood pressure. *Am J Cardiol* 1992;**70**:60D-66D
 173. De Bruijn JHB, Orofiamma BA, Pauly NC. Efficacy and tolerance of trandolapril (0.5-2mg) administered for 4 weeks in patients with mild-to-moderate hypertension. *J Cardiovasc Pharmacol* 1994;**23** (Suppl 4):S60-S64
 174. Messerli F, Frishman WH, Elliott WJ. Effects of verapamil and trandolapril in the treatment of hypertension. *Am J Hypertens* 1998;**11**:322-7
 175. Ford NF, Fulmor IE, Nichola PS, Alpin PG, Herron JM. Fosinopril monotherapy: relationship between blood pressure reduction and time of administration. *Clin Cardiol* 1993;**16**:324-30
 176. Pool JL. Antihypertensive effect of fosinopril, a new angiotensin converting enzyme inhibitor: findings of the Fosinopril Study Group II. *Clin Ther* 1990;**12**:520-33
 177. Anderson RJ, Duchin KL, Gore RD, Herman TS, Michaels RS, Nichola PS, et al. Once-daily fosinopril in the treatment of hypertension. *Hypertension* 1991;**17**:636-42
 178. Maclean D. Quinapril: a double-blind, placebo-controlled trial in essential hypertension. *Angiology* 1989;**40**:370-81
 179. Säynävalampi P, Pörsti I, Pörsti P, Nurmi A, Seppälä E, Manninen V, et al.

- Effects of the converting enzyme inhibitor quinapril on blood pressure, renin-angiotensin system and prostanoids in essential hypertension. *J Cardiovasc Pharmacol* 1988;12:88-93
180. Gupta RK, Kjeldsen SE, Motley E, Weder AB, Sweifler AJ, Julius S. Platelet function during antihypertensive treatment with quinapril, a novel angiotensin converting enzyme inhibitor. *J Cardiovasc Pharmacol* 1991;17:13-9
 181. Kjeldsen SE, Gupta RK, Krause L, Weder AB, Julius S. Does blood pressure reduction necessarily compromise cardiac function or renal hemodynamics? Effects of the angiotensin-converting enzyme inhibitor quinapril. *Am Heart J* 1992;123:1433-8
 182. Black HR, Graff A, Shute D, Stoltz R, Ruff D, Levine J, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. *J Hum Hypertens* 1997;11:483-9
 183. Paolisso G, Balbi V, Gambardella A, Varricchio G, Tortoriello R, Saccomanno F, et al. Lisinopril administration improves insulin action in aged patients with hypertension. *J Hum Hypertens* 1995;9:541-6
 184. Thürig C, Böhlen L, Schneider M, de Courten M, Shaw SG, Riesen W, et al. Lisinopril is neutral to insulin sensitivity and serum lipoproteins in essential hypertensive patients. *Eur J Clin Pharmacol* 1995;49:21-6
 185. Tomei R, Rossi L, Carbonieri E, Franceschini L, Molon G, Zardini P. Antihypertensive effect of lisinopril assessed by 24-hour ambulatory monitoring: a double-blind, placebo-controlled, cross-over study. *J Cardiovasc Pharmacol* 1992;19:911-14
 186. Polónia J, Martins L, Macedo F, Faria DB, Simões, Brandão F, et al. Lisinopril and diltiazem reduce left ventricular mass without changing blood pressure in normotensive subjects with exaggerated blood pressure response to exercise. *Rev Port Cardiol* 1996;15:185-93
 187. Gomez JH, Cirillo VJ, Sromovsky JA, Otterbein ES, Shaw WC, Rush JE, et al. Lisinopril dose-response relationship in essential hypertension. *Br J Clin Pharmacol* 1989;28:415-20
 188. Chan P, Lin C, Tomlinson B, Lin T, Lee Y. Additive effects of diltiazem and lisinopril in treatment of elderly patients with mild-to-moderate hypertension. *Am*

J Hypertens 1997;10:743-9

189. Burris JF. The effect of ramipril on ambulatory blood pressure: a multicenter study. *J Cardiovasc Pharmacol* 1991;18 (Suppl 2):S131-3
190. McCarron D. 24-hour blood pressure profiles in hypertensive patients administered ramipril or placebo once daily: magnitude and duration of antihypertensive effects. *Clin Cardiol* 1991;14:737-42
191. Schnaper HW. Dose-response relationship of ramipril in patients with mild-to-moderate hypertension. *J Cardiovasc Pharmacol* 1991;18 (Suppl 2):S128-S130
192. Homuth V, Faulhaber H, Loose U, Löffler K, Luft FC. Usefulness of piretanide plus ramipril for systemic hypertension: a multicenter trial. *Am J Cardiol* 1993;72:666-71
193. Villamil AS, Cairns V, Witte PU, Bertolasi CA. A double-blind study to compare the efficacy, tolerance and safety of two doses of the angiotensin converting enzyme inhibitor ramipril with placebo. *Am J Cardiol* 1987;59:110D-114D
194. Guitard C, Lohmann FW, Alfiero R, Ruina M, Alvisi V. Comparison of efficacy of spirapril and enalapril in control of mild-to-moderate hypertension. *Cardiovasc Drugs Ther* 1997;11:449-57
195. Guitard C, Sassano P, Tzincoca C, Duchiez J, Safar ME. Placebo-controlled crossover comparison of spirapril at 3, 6, 12 and 24 mg once daily in mild to severe essential hypertension. *Blood Press* 1994;3 (suppl 2):61-8
196. Guitard C, Alvisi V, Maibach E, Franck J, Cocco G, Boxho G, et al. Placebo-controlled comparison of spirapril at 6, 12 and 24 mg/day in mild to severe essential hypertension. *Blood Press* 1994;3 (suppl 2):81-7
197. Fairhurst GJ. A multicentre multidose study of the efficacy and safety of spirapril in mild-to-moderate essential hypertension. *Blood Press* 1994;3 (suppl 2):77-80
198. Frishman WH, Ram CVS, McMahon FG, Chrysant SG, Graff A, Kupiec JW, et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. *J Clin Pharmacol* 1995;35:1060-6
199. Kuschnir E, Acuña E, Sevilla D, Vasquez J, Bendersky M, Resk J, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 10 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. *Clin Ther* 1996;18:1213-24

200. Nawrocki JW, Weiss SR, Davidson MH, Sprecher DL, Schwartz SL, Lupien P-J, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol* 1995;15:678-82
201. Wald NJ, Law MR. Serum cholesterol and ischaemic heart disease. *Atherosclerosis* 1995; 118 (Suppl): 51-5.
202. Crouse JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis* 1998B138:11-24
203. Boysen G, Sørensen S, Juhler M, Andersen AR, Boas J, Oslen JS, et al. Danish very-low dose aspirin after carotid endarterectomy trial. *Stroke* 1988;19:1211-15
204. Sivenius J, Cunha L, Diener H-C, Forbes C, Laakso M, Lowenthal, et al. Second European stroke prevention study: antiplatelet therapy is effective regardless of age. *Act Neurol Scand* 1999;99:54-60
205. Juul-Möller S, Edvardsson N, Jahnmatz B, Rosén A, Sørensen S, Ömblus R, et al. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992;340:1421-5
206. The Salt Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* 1991;338:1345-9
207. Nyman I, Larsson H, Wallentin L, and The Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Prevention of serious cardiac events by low-dose aspirin in patients with silent myocardial ischaemia. *Lancet* 1992;340:497-501
208. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-30
209. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. *Lancet* 1989;1:175-9
210. Wallentin LC, The Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence

- of severe angina and the need for revascularization. *J Am Coll Cardiol* 1991;**18**:1587-93
211. Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, et al. Effects of aspirin and *trapidil* on cardiovascular events after acute myocardial infarction. *Am J Cardiol* 1999;**83**:1308-13
 212. Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation. *Am Heart J* 1999;**138**:137-43
 213. Meister W, v Schacky C, Weber M, Lorenz R, Kotzur J, Reichart B, et al. Low-dose acetylsalicylic acid (100 mg/day) after aortocoronary bypass surgery: a placebo-controlled trial. *Br J Clin Pharmacol* 1984;**17**:703-11
 214. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: a randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998;**351**:233-41
 215. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;**351**:1755-62
 216. Silagy CA, McNeil JJ, Donnan GA, Tonkin AM, Worsam B, Campion K. Adverse effects of low-dose aspirin in a healthy elderly population. *Clin Pharmacol Ther* 1993;**54**:84-9
 217. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ* 1998;**316**:894-8
 218. Wald NJ, Law M, Watt HC, Wu T, Bailey A, Johnson AM, et al. Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994;**343**:75-9

Claims

1. A formulation comprising active principals from at least two of the following four categories:
- 5 i) at least one blood pressure lowering agent,
- ii) at least one lipid-regulating agent,
- iii) at least one platelet function altering agent, and/or
- iv) at least one plasma/serum homocysteine lowering agent.
- 10 2. The formulation of claim 1, wherein blood pressure lowering agent is a diuretic, a beta blocker, an ACE inhibitor, an angiotension-II receptor antagonist, a vasodilator antihypertensive drug, and/or a calcium-channel blocker.
3. The formulation of claim 2, comprising one or more blood pressure lowering
- 15 agents selected from a diuretic, a beta blocker, and/or an ACE inhibitor.
4. The formulation of any one of the preceding claims, wherein the lipid-regulating agent is a statin.
- 20 5. The formulation of one of the any preceding claims, wherein the platelet function altering agent is aspirin, ticlopidine, dipyridamole, clopidogrel, a glycoprotein IIb/IIIa receptor inhibitor, or a non-steroidal anti-inflammatory drug.
6. The formulation of any one of the preceding claims, wherein the plasma/serum
- 25 homocysteine lowering agent is folic acid, vitamin B6, or vitamin B12.
7. The formulation of any one of the preceding claims, comprising:
 - i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
 - 30 ii) about 10 mg atorvastatin as a lipid-regulating agent,
 - iii) about 75 mg aspirin as a platelet function altering agent, and
 - iv) about 0.8 mg folic acid as a plasma/serum homocysteine lowering agent.

8. The formulation of any one of the preceding claims, further comprising an active principal from a fifth category comprising anti-oxidants.
9. The formulation of any one of the preceding claims, provided in a form suitable for
5 oral administration to a patient.
10. The formulation of any one of the preceding claims, wherein use of the formulation reduces the risk of cardiovascular disease by at least 80%.
- 10 11. Use of a formulation as claimed in any one of claims 1 to 10 for the manufacture of a medicament for the prevention of cardiovascular disease.
12. A method of preparing the formulation as claimed in any one of claims 1 to 10, comprising the steps of:
15 i) mixing the two or more active principals optionally with one or more pharmaceutically acceptable excipients, and
ii) forming the mixture into a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension suitable for oral administration to a patient.



INVESTOR IN PEOPLE

Application No: GB 0008791.6
Claims searched: 1-12

Examiner: Dr William Thomson
Date of search: 14 November 2000

Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:
UK Cl (Ed.R): A5B (BJA2)
Int Cl (Ed.7):
Other: ONLINE:CAS-ONLINE, EPODOC, JAPIO, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	WO 98/19690A1 (BRISTOL-MYERS SQUIBB CO) See whole document, in particular claims 16, 19, 21, 22 and 23	1-5 and 6 at least
X	WO 98/11896A1 (MERCK & CO INC) See whole document, in particular claims 13 and 23	1-5 and 6 at least
X	WO 97/38694 (MERCK & CO INC) See whole document, in particular claims 1-4 and 7	1-5 and 6 at least
X	Chemical Abstract No 131:153567 & C.D.Forbes et al, Semin. Thromb.Haemostasis, (1999), 25(suppl 2), 55-59 See Abstract	1 and 5 at least
X	Chemical Abstract No 129:339684 & C.Spaulding et al, Circulation, (1998), 98(8), 757-765 See abstract	1 and 5 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

GB2361185

Publication Title:

Pharmaceutical formulation for the prevention of cardiovascular disease

Abstract:

Abstract of GB2361185

A formulation for the prevention of cardiovascular disease, in particular ischaemic heart disease and stroke, the use of said formulation and a method of preparing said formulation. The said formulation is a combination of medicines contained in a single formulation for use in the prevention of cardiovascular disease, notably ischaemic heart disease (including heart attacks) and stroke among the general adult population. The said formulation comprises active principals from at least two of the following four categories of drugs or agents: <SL> i) a blood pressure lowering agent; ii) a lipid-regulating agent; iii) a platelet function altering agent; and/or iv) a plasma/serum homocysteine lowering agent. </SL> Data supplied from the esp@cenet database - Worldwide

Courtesy of <http://v3.espacenet.com>

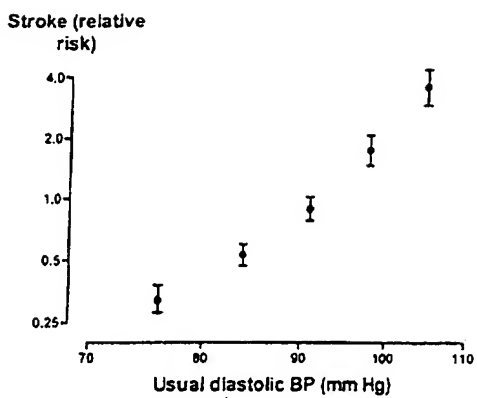


Fig. 1

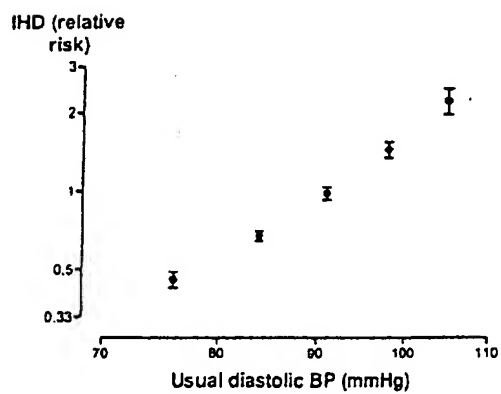


Fig. 2

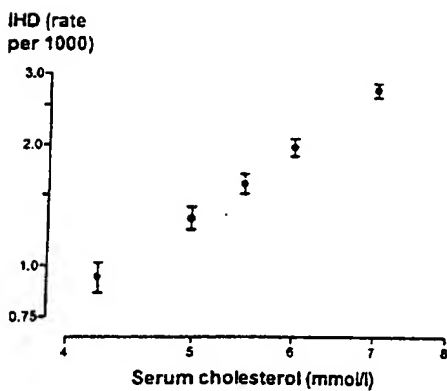


Fig. 3